Haas, M. E., Aragam, K. G., Emdin, C., Bick, A. G., Hemani, G., & Davey Smith, G., & Kathiresan, S. (2018). Genetic association of albuminuria with cardiometabolic disease and blood pressure. *American Journal of Human Genetics*, 461-473. https://doi.org/10.1016/j.ajhg.2018.08.004

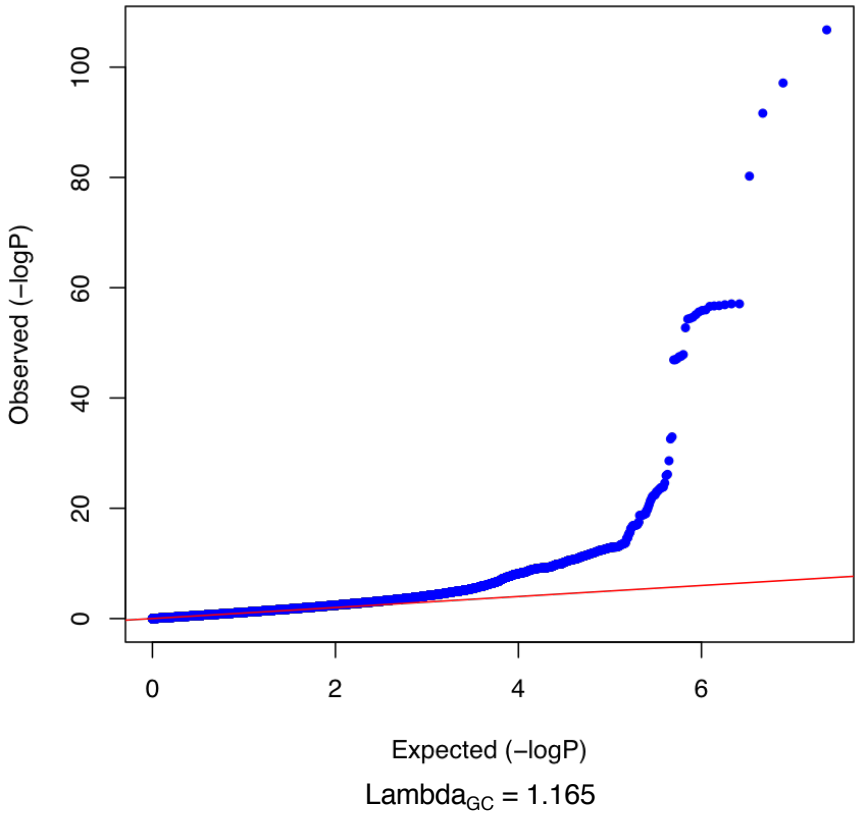


Figure S1. Genomic inflation in genome-wide association study of albuminuria in UK Biobank.

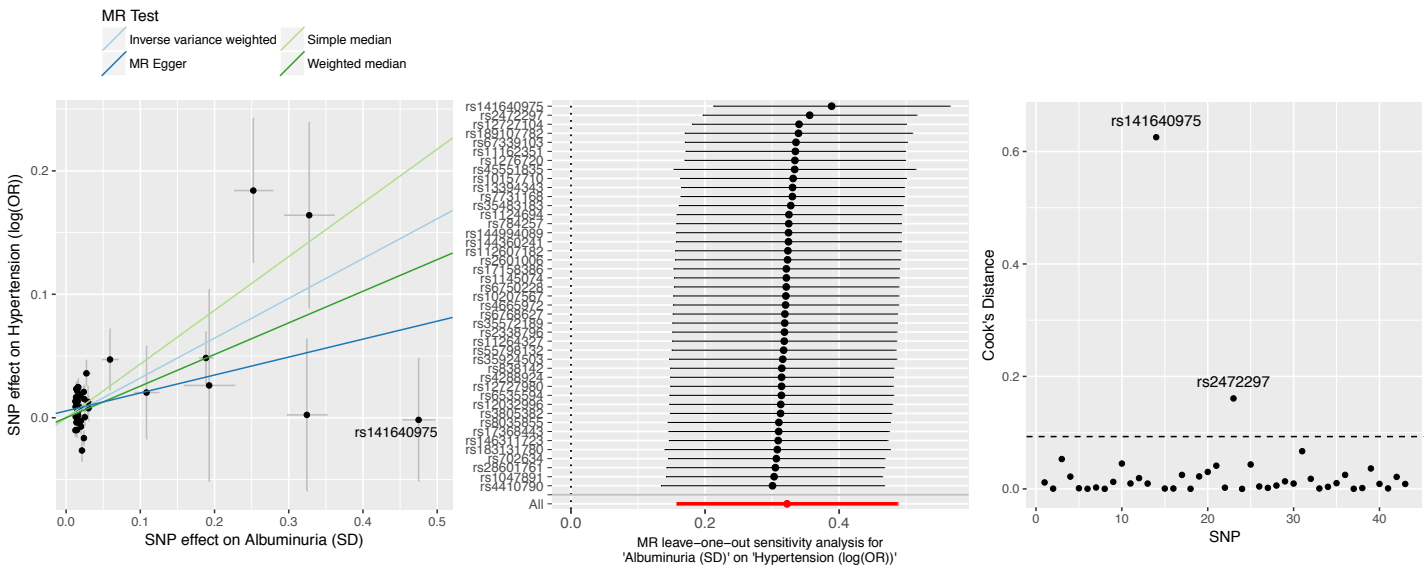
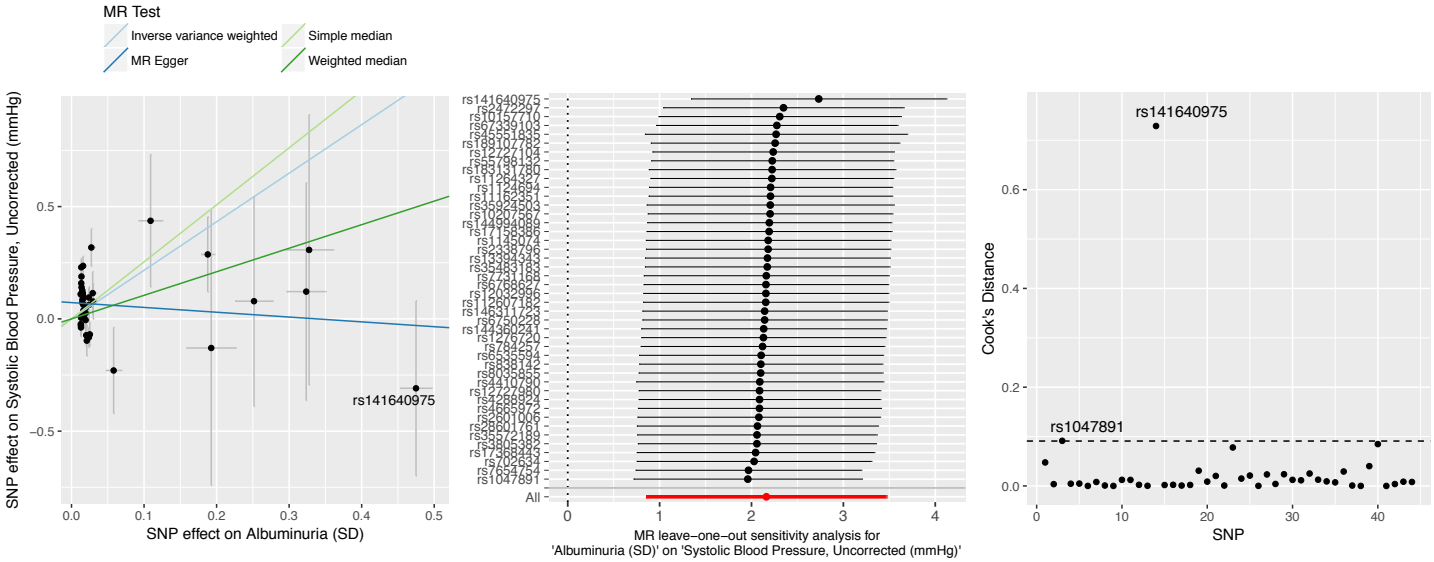


Figure S2. Sensitivity analyses for Mendelian randomization of 43-SNP albuminuria genetic risk score with hypertension in UK Biobank (n = 382500). Left, effect of each SNP on albuminuria and hypertension. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Albuminuria → Systolic Blood Pressure



Albuminuria → Diastolic Blood Pressure

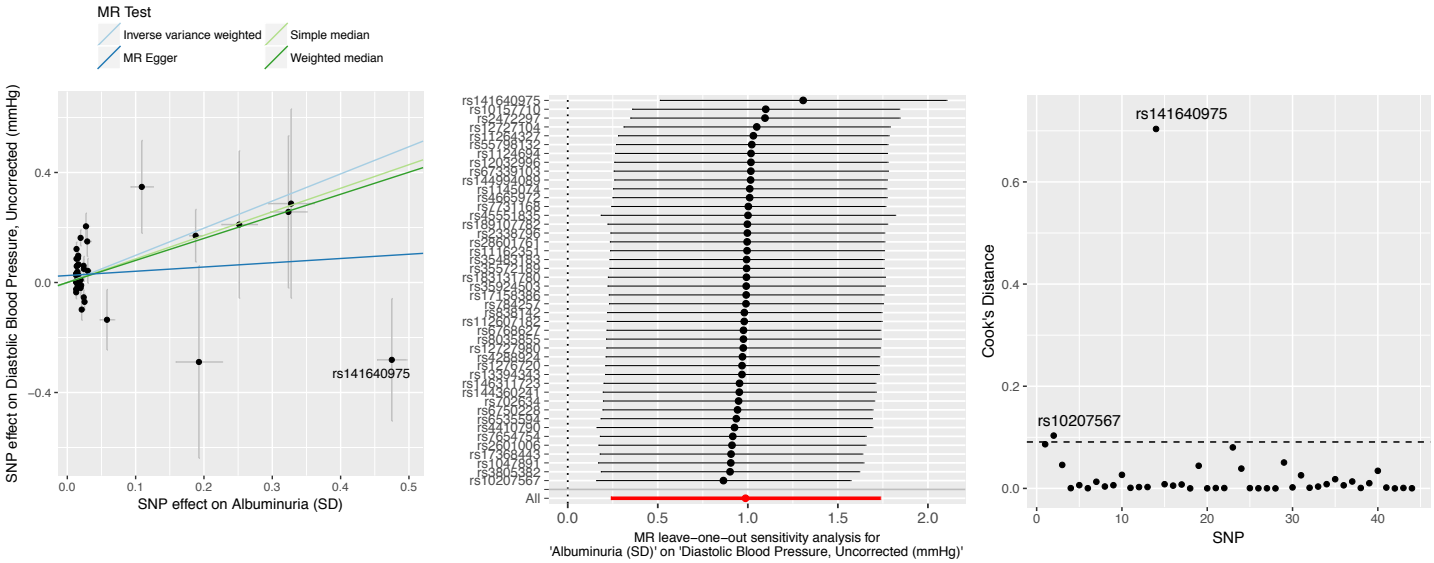
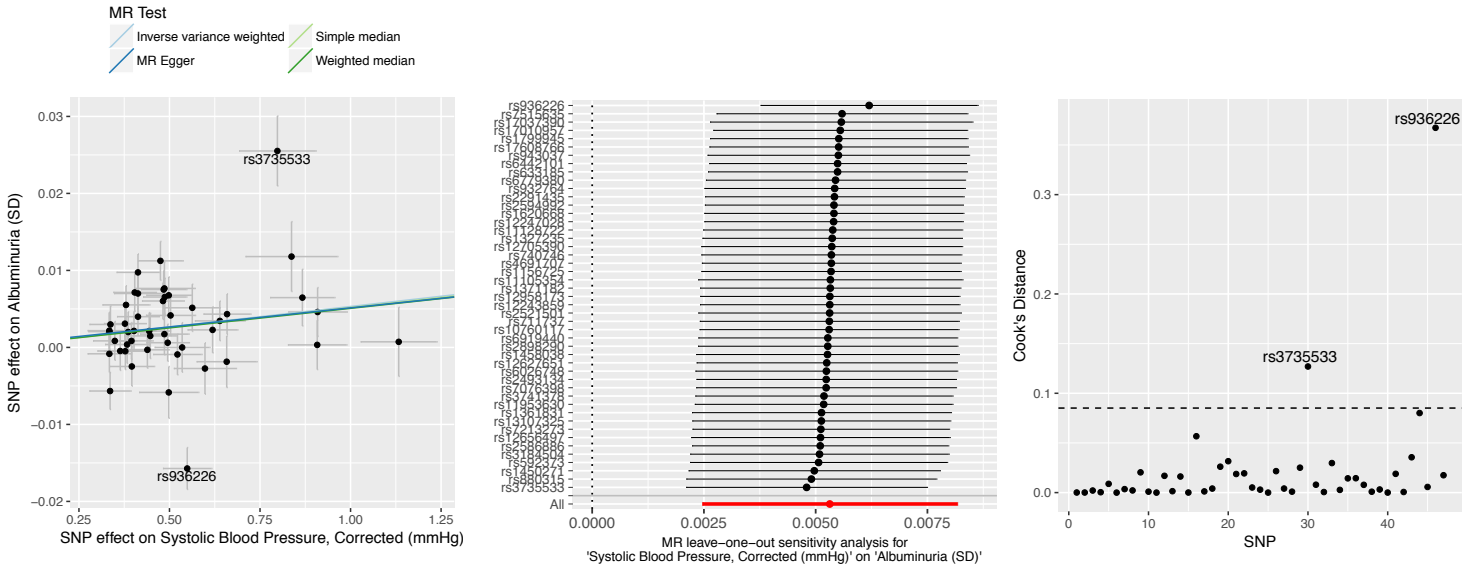


Figure S3. Sensitivity analyses for Mendelian randomization of 44-SNP albuminuria genetic risk score with blood pressure in UK Biobank (n = 381833). Neither blood pressure nor albuminuria were corrected for hypertensive medication use. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Systolic Blood Pressure → Albuminuria



Diastolic Blood Pressure → Albuminuria

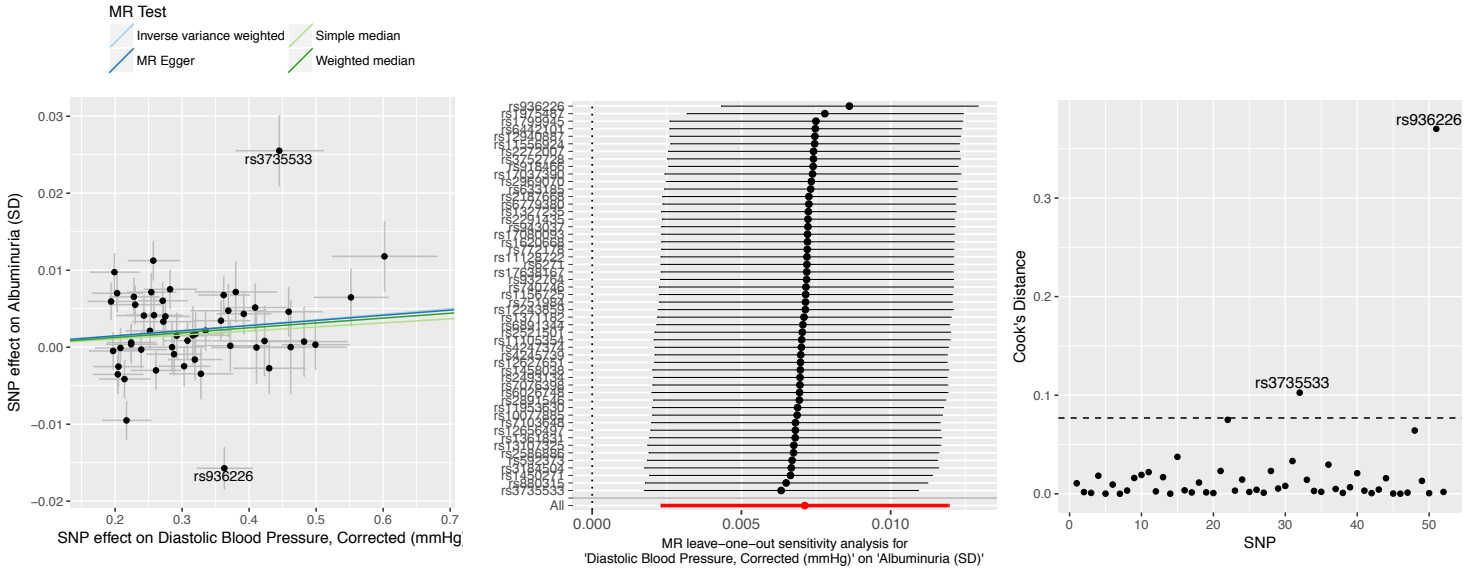
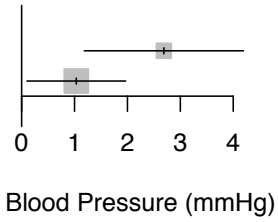


Figure S4. Sensitivity analyses for Mendelian randomization of blood pressure genetic risk scores from ICBP Cardio-MetaboChip (n_{max} = 201529) with albuminuria in UK Biobank (n = 382500). Blood pressures are corrected for hypertensive medication use and include BMI as covariate. Systolic blood pressure genetic risk score comprised of 47 SNPs, diastolic blood pressure genetic risk score comprised of 52 SNPs. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Exposure	Outcome	SNPs in score	mmHg Blood Pressure [95%CI] per 1–SD Increase in Albuminuria	P value
Albuminuria	Systolic Blood Pressure	37	2.69 [1.18; 4.19]	4.64e−04
Albuminuria	Diastolic Blood Pressure	35	1.03 [0.10; 1.97]	0.030



Exposure	Outcome	SNPs in score	mmHg Blood Pressure [95%CI] per 1–SD Increase in Albuminuria	P value
Albuminuria	Systolic Blood Pressure	22	1.46 [0.53; 2.38]	0.002
Albuminuria	Diastolic Blood Pressure	22	0.67 [0.14; 1.21]	0.013

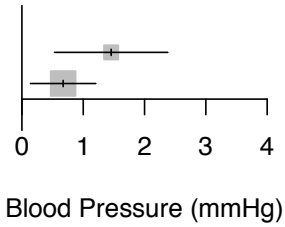
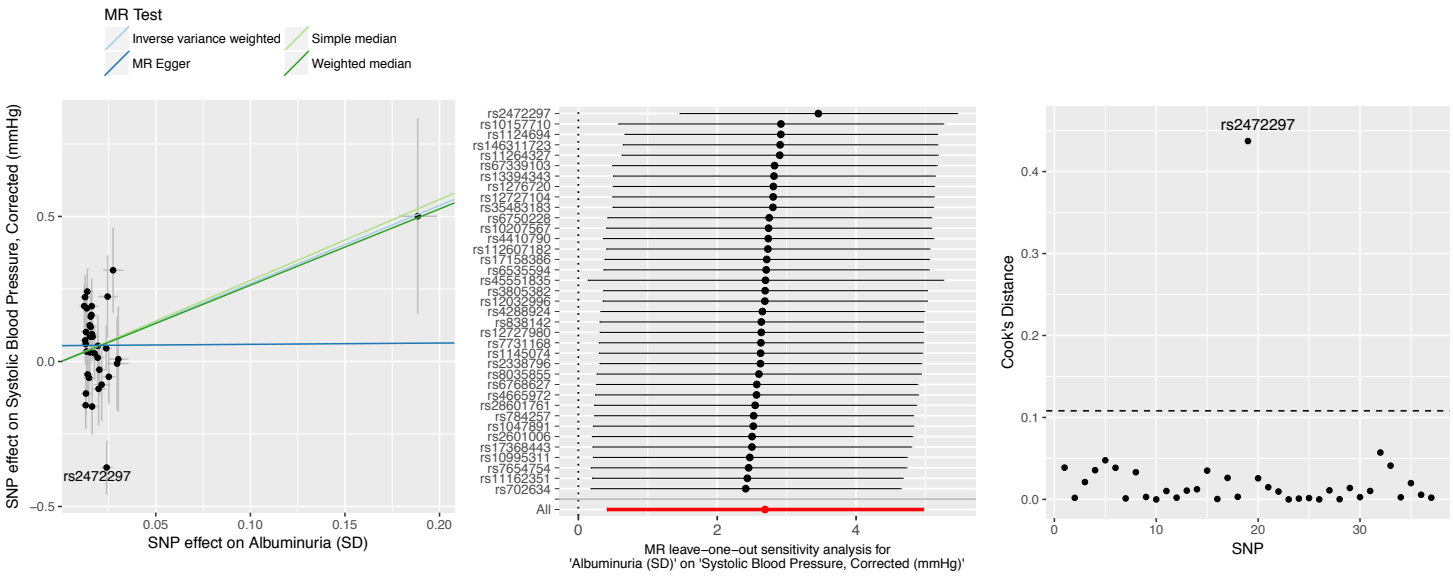


Figure S5. Additional Mendelian randomization analyses of albuminuria genetic risk score from UK Biobank with blood pressure outcomes.

SNPs in score, number of albuminuria variants after applying directional MR Steiger filtering to remove variants acting in the incorrect direction. Results are standardized to 1-SD increase in albuminuria due to the genetic risk score. Top, effect of albuminuria genetic risk score from UK Biobank (n = 382500) on blood pressure corrected for hypertensive medication use and BMI from ICBP 1000G (n_{max} = 150134) via inverse variance weighted fixed effect meta-analysis. Out of 46 albuminuria score SNPs, 38 were available in ICBP. Two sample Mendelian randomization analysis.

Bottom, Association of albuminuria genetic risk with blood pressure without hypertension medication effects in UK Biobank (n = 302687). Two-stage least-squares regression using albuminuria genetic risk score as instrumental variable on blood pressure outcomes in UK Biobank; age + sex + genotyping array + 1st 10 PCs as covariates. Individuals taking hypertensive medications were excluded. Bars indicate 95% confidence intervals for effect on blood pressure.

Albuminuria → Systolic Blood Pressure



Albuminuria → Diastolic Blood Pressure

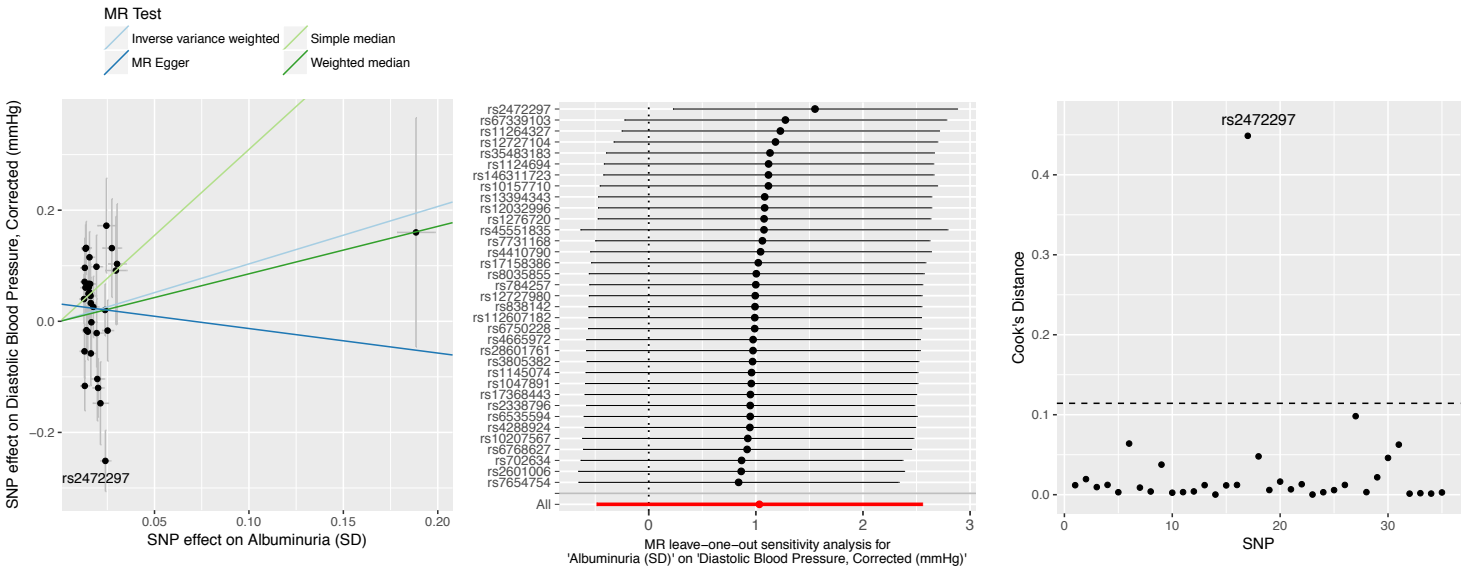
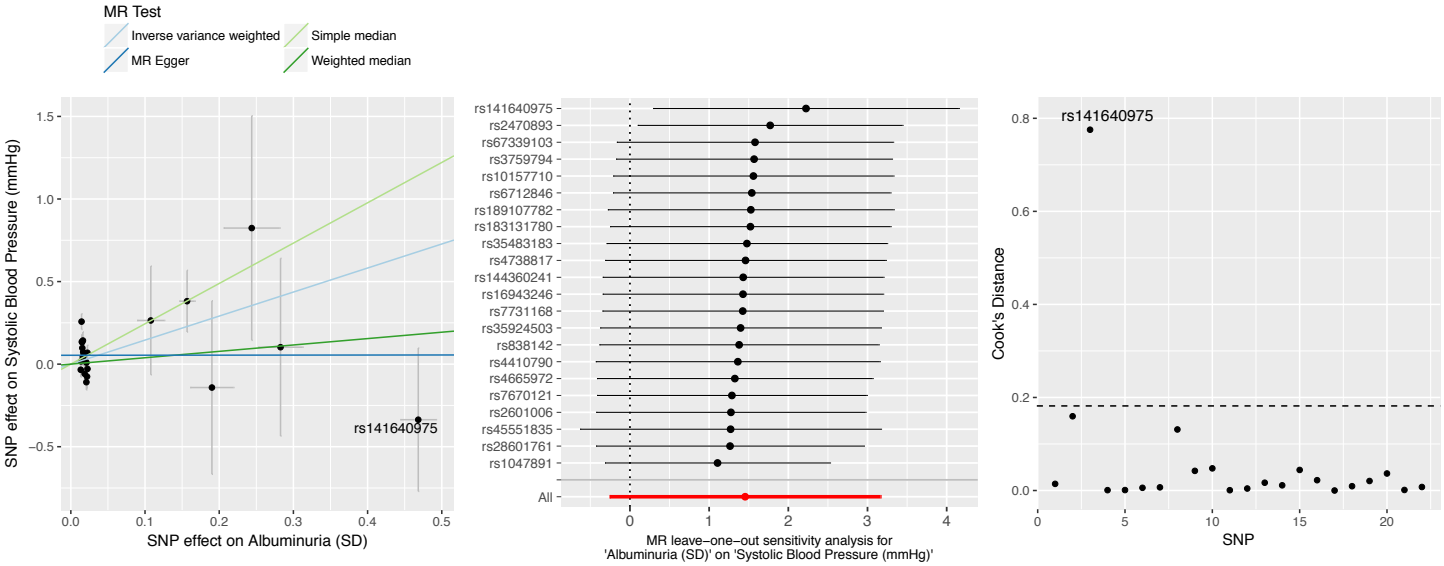


Figure S6. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score in UK Biobank (n = 382500) with Blood Pressure from ICBP 1000G (n_{max} = 150134). Blood pressures are corrected for hypertensive medication use and include BMI as covariate. Albuminuria genetic risk score comprised of 37 SNPs for systolic blood pressure outcome and 35 SNPs for diastolic blood pressure outcome. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Albuminuria → Systolic Blood Pressure



Albuminuria → Diastolic Blood Pressure

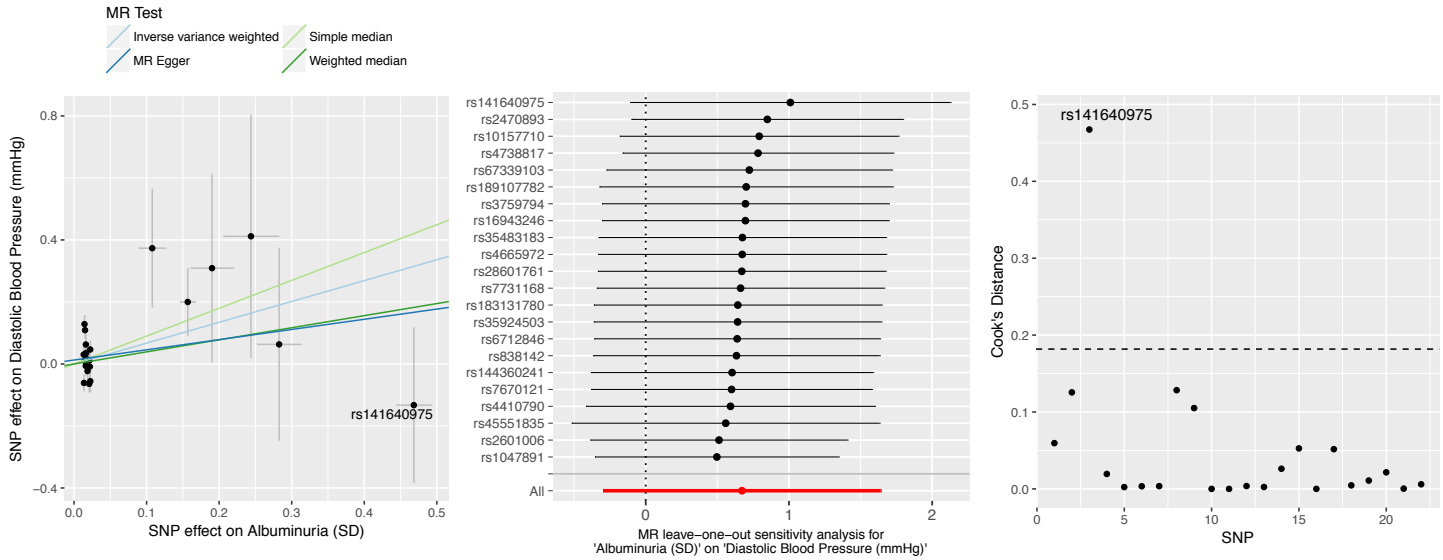


Figure S7. Sensitivity analyses for Mendelian randomization of 22-SNP albuminuria genetic risk score with blood pressure in UK Biobank (n = 302687). Individuals with hypertensive medication use were excluded. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Table S1. Characteristics of participants in UK Biobank.

No. Individuals	382500
Age, mean (SD), yrs	56.9 (7.9)
Women, No. (%)	204890 (53.6)
UK BiLEVE array, No. (%)	44806 (11.7)
Blood pressure, mean (SD), mmHg*	
Systolic	138.3 (18.6)
Diastolic	82.3 (10.1)
Body mass index, mean (SD)**	27.4 (4.7)
Current smoker, No. (%)***	39051 (10.2)
Urine albumin/creatinine, median (IQR), mg/g	9.8 (6.1-16.5)
Microalbuminuria, No. (%)	54519 (14.3)
Macroalbuminuria, No. (%)	1495 (0.4)
Coronary Artery Disease, No. (%)	32623 (8.5)
Type 2 Diabetes, No. (%)	17619 (4.6)
Hypertension, No. (%)	124345 (32.5)
Chronic Kidney Disease, No. (%)	4885 (1.3)

* Baseline blood pressure was averaged from two measurements taken a few moments apart and was unadjusted for hypertensive medication use. Measurements were missing from 667 and 656 individuals for systolic and diastolic blood pressure, respectively.

** Body mass index was calculated in units of kilograms weight divided by height in meters squared. Baseline measurement was missing for 1029 individuals

*** Excludes 1302 individuals for whom smoking status was not available

Table S2. Cardiometabolic Disease Definitions

Outcome	Definition
All-cause mortality	Death certificate provided by NHS Information Centre or NHS Central Register, Scotland
Coronary artery disease	Myocardial infarction (MI), angina, coronary artery bypass grafting, coronary artery angioplasty or triple heart bypass documented in medical history at time of enrollment by a trained nurse or Hospitalization for or death due to ICD-10 code for acute or subsequent myocardial infarction (I21, I21.0-21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0-23.6, I23.8) or ischaemic or atherosclerotic heart disease (I24, I24.0, I24.1, I24.8, I24.9, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9) or angina (I20, I20.0, I20.1, I20.8, I20.9) or Hospitalization for ICD-9 code due to myocardial infarction, ischaemic heart disease, angina, or coronary atherosclerosis (410, 4109, 411, 4119, 412, 4129, 413, 4139, 4140, 4148, 4149) or Hospitalization for OPCS-4 coded procedure: coronary artery bypass grafting (K40, K40.1-K40.4, K40.8, K40.9, K41, K41.1-41.4, K41.8, K41.9, K42, K42.1-K42.4, K42.8, K42.9, K43, K43.1-43.4, K43.8, K43.9, K44, K44.1, K44.2, K44.8, K44.9, K45.1-45.6, K45.8, K45.9, K46, K46.1-46.5, K46.8, K46.9) or Hospitalization for OPCS-4 coded procedure: coronary angioplasty ± stenting (K49.1-49.4, K49.8, K49.9, K50.1, K50.2, K50.4, K75.1-75.4, K75.8, K75.9)
Stroke	History of stroke, adjudicated centrally by UK Biobank as self-report of stroke during verbal interview with trained nurse or hospitalization for or death due to ICD-10 code I60-64 or ICD-9 code (430, 431, 434, 436) *(*df-42007, *http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=462)*
Peripheral vascular disease	Self-reported history of peripheral vascular disease, arterial embolism, intermittent claudication, leg artery bypass, leg artery angioplasty, or leg amputation during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for atherosclerosis of (non-coronary) arteries or peripheral vascular disease (I70.0, I70.00, I70.01, I70.2, I70.20, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8 or I73.9) or Hospitalization for ICD-9 code due to atherosclerosis of arteries or peripheral vascular disease (4400, 4402, 4438, 4439) or Hospitalization for OPCS-4 coded procedure for leg amputation, or leg artery procedure such as bypass, stent or angioplasty (X09.3-09.5, L21.6, L51.3, L51.6, L51.8, L52.1, L52.2, L54.1, L54.4, L54.8, L59.1-L59.8, L60.1, L60.2, L63.1, L63.5, L63.9, L66.7)
Heart failure	Self-reported history of heart failure or cardiomyopathy during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for hypertensive heart disease, cardiomyopathy or heart failure (I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.8, I42.9, I50, I50.0, I50.1, I50.9) or Hospitalization for ICD-9 code due to heart failure or other primary cardiomyopathies (4254, 4280, 4281, 4289) Note: Individuals with history of hypertrophic cardiomyopathy during verbal interview with trained nurse, or hospitalization for or death due to ICD-10 code for hypertrophic cardiomyopathy (I42.1, I42.2) were excluded from both case and control status
Type 2 diabetes	Self-reported history of type 2 diabetes during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for non-insulin-dependent diabetes mellitus (E11, E11.0-11.9)
Chronic kidney disease	Self-reported history of kidney failure ± dialysis, kidney nephropathy, IgA nephropathy, diabetic nephropathy or kidney transplant during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for hypertensive renal disease, chronic renal failure, end stage renal failure or chronic kidney disease (I12.0, I13.1, I13.2, N18, N18.0-18.5, N18.8, N18.9) or Hospitalization for ICD-9 code due to chronic renal failure (585, 5859) or Hospitalization for OPCS-4 coded procedure for kidney transplantation (M01, M01.1-01.5, M01.8, M01.9)
Hypertension	Self-reported history of hypertension, essential hypertension or high blood pressure during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for essential hypertension, hypertensive heart disease, hypertensive renal disease, secondary hypertension or renovascular hypertension (I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0-13.2, I15, I15.0-15.2, I15.8, I15.9) or Hospitalization for ICD-9 code due to essential hypertension, hypertensive heart disease, hypertensive renal disease, or secondary hypertension (403, 4030, 4031, 4039, 404, 4040, 4041, 405, 4050, 4051, 4059)

Skin cancer	Self-reported history of skin cancer, malignant melanoma, non-melanoma skin cancer, basal cell carcinoma or squamous cell carcinoma during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for malignant melanoma, skin, or malignant neoplasm of skin (C43, C43.2-43.7, C43.9, C44, C44.0-44.9) or Hospitalization for ICD-9 code due to malignant melanoma or malignant neoplasm of skin (172, 1727, 173, 1733, 1735, 1739)
Baseline diabetes	Self-reported history of diabetes, gestational diabetes, type1 diabetes, or type 2 diabetes, insulin medication use, or began insulin within one year of diabetes diagnosis during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for insulin-dependent diabetes, non-insulin-dependent diabetes mellitus, malnutrition-realted diabetes or other diabetes (E10, E10.0-10.9, E11, E11.0-11.9, E12, E12.1, E12.8, E12.9, E13, E13.1-13.3, E13.5-13.9, E14, E14.0-14.9) or Hospitalization for ICD-9 code due to diabetes mellitus with mention with complication, diabetes with ketoacidosis or renal, opthalmic or neurological manifestations or unspecified complications (2500, 25000, 25001, 25009, 2501, 25011, 25019, 250302505, 25099)
Baseline hyperlipidemia	Self-reported history of high cholesterol during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for hypercholesterolaemia, hyperglyceridaemia, or hyperlipidaemia (E78.0-E78.2, E78.4, E78.5)

Data fields used in definitions: self-report, df-20002, df-20004, df-6150, df-2986, df-6153, df-6177; ICD9, df-41203, df-41205; ICD10, df-41202, df-41204, df-40001, df-40002; OPCS-4 procedures, df-41200, df-41210; death registry, df-40001, df-40002.

Table S3. Comparison of lead albuminuria variants in UK Biobank with effects in CKDGen.

					UK Biobank				CKDGen (Teumer *et al* 2016)					
rsid	Proxy to	R^2 with Proxy	Effect Allele	Noneffect Allele	EAF	Beta (log(mg/g))	SE (log(mg/g))	P value	EAF	Beta (log(mg/g))	SE (log(mg/g))	P value	N	Direction, UKB & CKDGen?
rs10157710			T	C	0.802	0.019	0.0021	9.69E-20	0.695	0.015	0.007	**0.045**	54449	same
rs12032996			G	A	0.838	0.015	0.0023	9.33E-11	0.85	0.010	0.008	0.220	54450	same
rs1276720			T	C	0.745	0.011	0.0019	8.98E-09	0.783	0.007	0.008	0.360	53465	same
rs17158386			A	G	0.262	0.013	0.0019	3.65E-12	0.215	0.020	0.009	**0.029**	53465	same
rs2023844			A	G	0.926	0.019	0.0032	1.18E-09	0.945	0.036	0.014	**0.009**	54450	same
rs2472297			T	C	0.267	0.018	0.0019	5.31E-22	0.248	0.002	0.009	0.830	54450	same
rs2601006			C	T	0.657	0.012	0.0018	2.13E-11	0.637	-0.001	0.007	0.850	54448	opposite
rs4410790			C	T	0.634	0.018	0.0017	2.63E-25	0.58	0.001	0.007	0.860	54450	same
rs6535594			A	G	0.495	0.011	0.0017	7.12E-12	0.487	0.018	0.007	**0.006**	54390	same
rs702634			A	G	0.693	0.010	0.0018	8.03E-09	0.708	0.005	0.006	0.400	54415	same
rs7654754			G	A	0.463	0.010	0.0017	9.96E-10	0.478	0.012	0.006	**0.043**	54382	same
rs8035855			A	G	0.644	0.012	0.0017	1.91E-12	0.694	0.003	0.007	0.640	54448	same
rs1971819	rs10207567	0.999	C	G	0.813	0.014	0.0021	1.44E-11	0.8	0.015	0.008	0.052	53368	same
rs715	rs1047891	0.939	T	C	0.688	0.011	0.0018	1.02E-09	0.708	0.012	0.009	0.170	43892	same
rs1260326	rs4665972	0.93	T	C	0.393	0.011	0.0017	3.12E-11	0.42	0.022	0.006	**2.70E-04**	54441	same
rs17026396	rs13394343	1	T	C	0.570	0.011	0.0017	4.15E-10	0.553	0.005	0.006	0.380	54441	same
rs2044474	rs13394343	1	G	A	0.570	0.011	0.0017	4.16E-10	0.515	0.005	0.006	0.400	54440	same
rs6547620	rs13394343	1	C	T	0.570	0.011	0.0017	3.97E-10	0.537	0.004	0.006	0.460	54439	same
rs6739015	rs13394343	1	A	G	0.570	0.011	0.0017	3.96E-10	0.558	0.005	0.006	0.380	54441	same
rs11960938	rs7731168	0.962	A	G	0.236	0.012	0.0020	1.06E-09	0.25	-0.007	0.008	0.370	53378	opposite
rs7915302	rs67339103	0.955	C	T	0.219	0.015	0.0020	2.39E-13	0.23	0.004	0.007	0.550	54450	same
rs17295800	rs17368443	0.996	C	T	0.061	0.020	0.0035	6.40E-09	0.062	0.015	0.013	0.250	54450	same
rs2920154	rs17368443	0.996	C	T	0.061	0.020	0.0035	4.98E-09	0.071	0.022	0.014	0.110	53465	same
rs10873217	rs4288924	0.999	G	A	0.480	0.010	0.0017	6.48E-09	0.504	0.008	0.006	0.190	54399	same
rs1153849	rs1145074	0.997	G	A	0.745	0.011	0.0019	3.58E-09	0.79	0.010	0.007	0.130	54450	same
rs1346266	rs1145074	0.997	G	T	0.745	0.011	0.0019	3.53E-09	0.797	0.007	0.007	0.310	44877	same
rs4021	rs838142	0.995	A	G	0.723	0.012	0.0019	6.25E-10	0.761	0.025	0.009	**0.004**	53465	same

Table S4. Forty-six variants included in Mendelian randomization analyses.

Lead variant	Nearest Gene(s)	Description	Chr	Position (hg19)	Effect Allele	Noneffect Allele	EAF	Beta (log(mg/g))	SE (log (mg/g))	P value
rs12032996	*PHC2-ZSCAN20*	Intergenic	1	33920586	G	A	0.838	0.01463	0.00226	9.33E-11
rs10157710	*FOXD2-TRABD2B*	Intergenic	1	47961691	T	C	0.802	0.019	0.00209	9.69E-20
rs11162351	*AK5*	Intronic	1	77944732	C	G	0.602	0.00952	0.0017	2.20E-08
rs11264327	*EFNA3-EFNA1*	Intergenic	1	155095107	A	G	0.399	0.00987	0.00171	7.03E-09
rs12727104	*FMO4-PRRC2C*	Intergenic	1	171423167	G	A	0.905	0.01614	0.00284	1.37E-08
rs12727980	*NR5A2-LINC00862*	Intergenic	1	200259095	C	T	0.423	0.00957	0.0017	1.68E-08
rs4665972	*SNX17*	Intronic	2	27598097	T	C	0.393	0.01176	0.00172	6.96E-12
rs6750228	*LOC730100*	Intronic	2	51312124	A	T	0.047	0.02232	0.00398	2.07E-08
rs13394343	*SH2D6-MAT2A/PARTICL*	Intergenic	2	85754342	C	A	0.57	0.01053	0.00168	3.86E-10
rs10207567	*ICA1L*	Intronic	2	203714973	C	G	0.813	0.01455	0.00214	1.00E-11
rs1047891	*CPS1*	Missense	2	211540507	C	A	0.684	0.01205	0.00179	1.71E-11
rs183131780	*MIR548AR-LOC646736*	Intergenic	2	226684886	T	C	0.002	0.19055	0.01959	2.33E-22
rs35483183	*COL4A4*	Intronic	2	227876687	A	G	0.123	0.0149	0.00255	5.19E-09
rs35924503	*SPHKAP-PID1*	Intergenic	2	229131286	C	T	0.001	0.24742	0.02518	8.68E-23
rs6768627	*MYL3*	Downstream Variant	3	46895376	T	C	0.069	0.01852	0.0033	2.06E-08
rs112607182	*PRKCI*	Downstream Variant	3	170027407	T	C	0.077	0.02279	0.00327	3.39E-12
rs3805382	*NMU*	Intronic	4	56471551	A	G	0.711	0.01015	0.00184	3.71E-08
rs7654754	*SHROOM3*	Intronic	4	77409795	G	A	0.462	0.0102	0.00167	9.96E-10
rs6535594	*NR3C2*	Intronic	4	149132756	A	G	0.496	0.01146	0.00167	7.12E-12
rs189107782	*LINC01262-FRG1*	Intergenic	4	190729009	T	C	0.002	0.24502	0.02026	1.12E-33
rs702634	*ARL15*	Intronic	5	53271420	A	G	0.692	0.01042	0.00181	8.03E-09
rs7731168	*CWC27*	Intronic	5	64296471	C	G	0.233	0.01253	0.00197	2.19E-10
rs4410790	*AGR3-AHR*	Intergenic	7	17284577	C	T	0.634	0.01798	0.00173	2.63E-25
rs2023844	*HOTTIP*	Intronic	7	27243238	A	G	0.926	0.01934	0.00318	1.18E-09
rs17158386	*WIPF3-DPY19L2P3*	Intergenic	7	29805361	A	G	0.262	0.0133	0.00191	3.65E-12
rs55798132	*LOC101927815-CSMD1*	Intergenic	8	2666143	G	A	0.989	0.04472	0.00803	2.53E-08
rs28601761	*TRIB1-LINC00861*	Intergenic	8	126500031	C	G	0.579	0.01136	0.00171	2.81E-11
rs144994089	*AQP7*	Missense	9	33385156	T	C	0.001	0.1456	0.02562	1.32E-08
rs45551835	*CUBN*	Missense	10	16932384	A	G	0.014	0.14237	0.00698	2.28E-92
rs144360241	*CUBN*	Missense	10	16967417	C	T	0.005	0.08186	0.01234	3.31E-11
rs1276720	*CUBN*	Intronic	10	16971426	T	C	0.745	0.01109	0.00193	8.98E-09
rs141640975	*CUBN*	Missense	10	16992011	A	G	0.003	0.35876	0.01629	1.75E-107
rs10995311	*ADO*	Missense	10	64564934	C	G	0.553	0.00921	0.00168	4.49E-08
rs67339103	*C10orf11*	Intronic	10	77893686	A	G	0.212	0.01522	0.00205	1.07E-13
rs17368443	*SBF2*	Intronic	11	10296836	C	G	0.061	0.02071	0.00348	2.58E-09
rs1124694	*ZBED5AS1-GALNT18*	Intergenic	11	11098676	G	A	0.331	0.00977	0.00178	4.43E-08
rs2601006	*CCT2*	5' UTR Variant	12	69979517	C	T	0.657	0.01176	0.00176	2.13E-11
rs4288924	*ZFP36L1-ACTN1*	Intergenic	14	69302399	G	A	0.48	0.0098	0.00168	5.66E-09
rs8035855	*MAPKBP1*	Intronic	15	42077961	A	G	0.644	0.01227	0.00174	1.91E-12
rs1145074	*SPATA5L1*	Intronic	15	45703824	T	A	0.745	0.0114	0.00191	2.41E-09
rs146311723	*USP3*	Intronic	15	63804507	C	T	0.174	0.01231	0.0022	2.25E-08
rs2472297	*CYP1A2-CYP1A1*	Intergenic	15	75027880	T	C	0.267	0.01812	0.00188	5.31E-22
rs2338796	*FBXL20*	Intronic	17	37555627	A	G	0.67	0.00989	0.00178	2.59E-08
rs35572189	*BAHCC1*	Missense	17	79419025	G	A	0.638	0.01051	0.00174	1.44E-09
rs784257	*TCF4-LINC01415*	Intergenic	18	53397199	T	C	0.187	0.01218	0.00215	1.37E-08
rs838142	*FUT1*	3' UTR Variant	19	49252151	A	G	0.723	0.01174	0.00187	3.13E-10

Chr, chromosome; EAF, effect allele frequency. For intergenic loci, nearest upstream and downstream RefSeq genes are indicated. Nearest gene should not be taken as evidence of causal gene. Description, most-severe consequence of nearest RefSeq gene.

Table S5. Association of albuminuria genetic risk score with measured albuminuria in ARIC and Framingham Heart Study.

Cohort	Beta (log(mg/g) Albuminuria per SD predicted Albuminuria)	Std. Error (log(mg/g) Albuminuria per SD predicted Albuminuria)	P value
UK Biobank (reference)	0.742	0.014	< 1E-300
ARIC	0.788	0.198	6.72E-05
Framingham Heart Study	0.692	0.197	4.38E-04

Table S6. Sensitivity analyses for Mendelian randomization of restricted albuminuria genetic risk score with hypertension or blood pressure in UK Biobank.

Sample Size[a]	Number of Hypertension Cases	Number of Controls	Exposure	Outcome	SNPs in score	Method	Beta (log(OR)/SD Albuminuria)	SE (log(OR)/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
382500	124345	258155	Albuminuria	Hypertension	31	Two-Stage Least-Squares	0.313	0.046	1.01E-11				
382500	124345	258155	Albuminuria	Hypertension	31	IVW Random Effects	0.314	0.091	0.001	118	2E-12	128	< 1E-5
382500	124345	258155	Albuminuria	Hypertension	31	Simple Median	0.433	0.103	2.80E-05				
382500	124345	258155	Albuminuria	Hypertension	31	Weighted Median	0.256	0.088	0.003				
382500	124345	258155	Albuminuria	Hypertension	31	Egger Slope	0.134	0.126	0.289				
382500	124345	258155	Albuminuria	Hypertension	31	Egger Intercept	0.006	0.003	0.047				

Sample Size, Exposure[b]	Sample Size, Outcome[c]	Exposure	Outcome	SNPs in score	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
382500	381833	Albuminuria	SBP, Uncorrected	32	Two-Stage Least-Squares	2.191	0.361	1.26E-09				
382500	381833	Albuminuria	SBP, Uncorrected	32	IVW Random Effects	2.187	0.771	0.005	142	4E-16	154	< 1E-5
382500	381833	Albuminuria	SBP, Uncorrected	32	Simple Median	2.539	0.778	0.001				
382500	381833	Albuminuria	SBP, Uncorrected	32	Weighted Median	1.306	0.641	0.042				
382500	381833	Albuminuria	SBP, Uncorrected	32	Egger Slope	-0.187	0.974	0.847				
382500	381833	Albuminuria	SBP, Uncorrected	32	Egger Intercept	0.080	0.024	0.001				
382500	381833	Albuminuria	DBP, Uncorrected	32	Two-Stage Least-Squares	0.974	0.207	2.62E-06				
382500	381833	Albuminuria	DBP, Uncorrected	32	IVW Random Effects	0.972	0.414	0.019	125	3E-13	136	< 1E-5
382500	381833	Albuminuria	DBP, Uncorrected	32	Simple Median	0.889	0.385	0.021				
382500	381833	Albuminuria	DBP, Uncorrected	32	Weighted Median	0.830	0.364	0.022				
382500	381833	Albuminuria	DBP, Uncorrected	32	Egger Slope	0.207	0.582	0.722				
382500	381833	Albuminuria	DBP, Uncorrected	32	Egger Intercept	0.026	0.014	0.071				

Restricted albuminuria genetic risk composed of SNPs with $p < 9E-9$ for association with albuminuria + directional MR Steiger filtering (filtered to SNPs with R^2 exposure > R^2 outcome)
SBP, systolic blood pressure; DBP, diastolic blood pressure. Uncorrected, not adjusted for hypertensive medication use.
[a] Effects of SNPs on albuminuria and hypertension were calculated in 382500 individuals in UK Biobank
[b] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank
[c] 381833 individuals in UK Biobank had blood pressure measurements

Table S7. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score with hypertension in UK Biobank.

Sample Size[a]	Number of Hypertension Cases	Number of Controls	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (log(OR)/SD Albuminuria)	SE (log(OR)/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Directional MR Steiger filtering														
382500	124345	258155	Albuminuria	Hypertension	43	NA	Two-Stage Least-Squares	0.321	0.043	7.01E-14				
382500	124345	258155	Albuminuria	Hypertension	43, unweighted allele score	NA	Two-Stage Least-Squares	0.463	0.058	1.17E-15				
382500	124345	258155	Albuminuria	Hypertension	43	NA	IVW Random Effects	0.322	0.084	1.25E-04	160	9E-16	171	< 1E-05
382500	124345	258155	Albuminuria	Hypertension	43	NA	Simple Median	0.435	0.093	2.91E-06				
382500	124345	258155	Albuminuria	Hypertension	43	NA	Weighted Median	0.257	0.087	0.003				
382500	124345	258155	Albuminuria	Hypertension	43	NA	Egger Slope	0.145	0.123	0.235				
382500	124345	258155	Albuminuria	Hypertension	43	NA	Egger Intercept	0.006	0.003	0.053				
Directional MR Steiger filtering + Outlier removed														
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Two-Stage Least-Squares	0.389	0.047	2.65E-16				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	IVW Random Effects	0.389	0.090	1.50E-05	149	4E-14	156	< 1E-05
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Simple Median	0.446	0.091	9.92E-07				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Weighted Median	0.276	0.084	0.001				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Egger Slope	0.238	0.153	0.120				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Egger Intercept	0.004	0.003	0.222				
Significant directional MR Steiger filtering														
382500	124345	258155	Albuminuria	Hypertension	35	NA	Two-Stage Least-Squares	0.235	0.045	2.00E-07				
382500	124345	258155	Albuminuria	Hypertension	35	NA	IVW Random Effects	0.236	0.071	9.13E-04	84	4E-06	91	< 1E-05
382500	124345	258155	Albuminuria	Hypertension	35	NA	Simple Median	0.385	0.089	1.66E-05				
382500	124345	258155	Albuminuria	Hypertension	35	NA	Weighted Median	0.256	0.082	0.002				
382500	124345	258155	Albuminuria	Hypertension	35	NA	Egger Slope	0.177	0.103	0.087				
382500	124345	258155	Albuminuria	Hypertension	35	NA	Egger Intercept	0.002	0.003	0.421				
Significant directional MR Steiger filtering + Outlier removed														
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Two-Stage Least-Squares	0.291	0.051	8.17E-09				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	IVW Random Effects	0.292	0.077	1.54E-04	78	2E-05	83	2E-05
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Simple Median	0.397	0.089	7.43E-06				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Weighted Median	0.266	0.090	0.003				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Egger Slope	0.285	0.127	0.025				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Egger Intercept	2.02E-04	0.003	0.944				

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

Significant directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome AND Steiger P value < 0.05

[a] Effects of SNPs on albuminuria and hypertension were calculated in 382500 individuals in UK Biobank

Table S8. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score with blood pressure in UK Biobank.

Sample Size, Exposure[a]	Sample Size, Outcome[b]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure													
Directional MR Steiger filtering													
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Two-Stage Least-Squares	2.165	0.336	1.22E-10				
382500	381833	Albuminuria	SBP, Uncorrected	44, unweighted allele score	NA	Two-Stage Least-Squares	3.988	0.445	3.22E-19				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	IVW Random Effects	2.160	0.666	0.001	169	7E-17	180	< 1E-05
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Simple Median	2.539	0.689	2.29E-04				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Weighted Median	1.306	0.621	0.035				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Egger Slope	-0.209	0.900	0.817				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Egger Intercept	0.072	0.021	4.65E-04				
Directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Two-Stage Least-Squares	2.734	0.369	1.32E-13				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	IVW Random Effects	2.728	0.707	1.15E-04	155	7E-15	162	< 1E-05
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Simple Median	2.553	0.716	3.67E-04				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Weighted Median	1.530	0.665	0.021				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Egger Slope	0.137	1.134	0.904				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Egger Intercept	0.067	0.024	0.005				
Significant directional MR Steiger filtering													
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Two-Stage Least-Squares	1.375	0.348	7.8E-05				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	IVW Random Effects	1.372	0.518	0.008	85	2.0E-05	91	3.0E-05
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Simple Median	1.523	0.660	0.021				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Weighted Median	0.928	0.592	0.117				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Egger Slope	-0.037	0.709	0.958				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Egger Intercept	0.046	0.017	0.007				
Significant directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Two-Stage Least-Squares	1.818	0.385	2.26E-06				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	IVW Random Effects	1.814	0.554	0.001	77	0.00011	81	0.00015
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Simple Median	1.863	0.652	0.004				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Weighted Median	1.439	0.673	0.032				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Egger Slope	0.382	0.892	0.669				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Egger Intercept	0.039	0.019	0.046				
Diastolic Blood Pressure													
Directional MR Steiger filtering													
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Two-Stage Least-Squares	0.986	0.193	3.40E-07				
382500	381833	Albuminuria	DBP, Uncorrected	44, unweighted allele score	NA	Two-Stage Least-Squares	1.627	0.256	1.94E-10				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	IVW Random Effects	0.984	0.381	0.010	169	6E-17	180	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Simple Median	0.856	0.354	0.016				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Weighted Median	0.819	0.352	0.020				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Egger Slope	0.150	0.559	0.788				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Egger Intercept	0.025	0.013	0.048				

Directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Two-Stage Least-Squares	1.305	0.212	8.08E-10				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	IVW Random Effects	1.302	0.405	0.001	156	5E-15	162	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Simple Median	0.876	0.366	0.017				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Weighted Median	0.886	0.367	0.016				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Egger Slope	0.613	0.697	0.379				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Egger Intercept	0.018	0.015	0.226				
Significant directional MR Steiger filtering													
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Two-Stage Least-Squares	0.613	0.199	0.002				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	IVW Random Effects	0.611	0.314	0.051	99	4E-07	106	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Simple Median	0.772	0.349	0.027				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Weighted Median	0.791	0.343	0.021				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Egger Slope	0.148	0.461	0.749				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Egger Intercept	0.015	0.011	0.173				
Significant directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	DBP, Uncorrected	39	0.69	Two-Stage Least-Squares	0.873	0.219	6.93E-05				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	IVW Random Effects	0.870	0.336	0.010	91	3E-06	95	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Simple Median	0.791	0.357	0.027				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Weighted Median	0.879	0.371	0.018				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Egger Slope	0.602	0.571	0.292				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Egger Intercept	0.007	0.012	0.559				

SBP, systolic blood pressure; DBP, diastolic blood pressure. Uncorrected, not adjusted for hypertensive medication use.

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

Significant directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome AND Steiger P value < 0.05

[a] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank

[b] 381833 individuals in UK Biobank had blood pressure measurements

Table S9. Sensitivity analyses for Mendelian randomization of blood pressure genetic risk scores from ICBP Cardio-MetaboChip with albuminuria in UK Biobank.

Sample Size, Exposure[a]	Sample Size, Outcome[b]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	SNP in LD removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure														
Directional MR Steiger filtering														
201529	381833[c]	SBP, Corrected	Albuminuria	47	NA	NA	Two-Stage Least-Squares	0.0050	0.0007	2.45E-13				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	IVW Random Effects	0.0053	0.0015	2.55E-04	157	5E-14	164	< 1E-5
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Simple Median	0.0052	0.0013	6.15E-05				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Weighted Median	0.0051	0.0013	5.44E-05				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Egger Slope	0.0050	0.0051	0.331				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Egger Intercept	0.0002	0.0025	0.941				
Directional MR Steiger filtering + Outlier removed														
201529	381833[c]	SBP, Corrected	Albuminuria	46	0.37	NA	Two-Stage Least-Squares	0.0058	0.0007	3.19E-17				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	IVW Random Effects	0.0062	0.0012	5.64E-07	109	3E-07	113	< 1E-5
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Simple Median	0.0053	0.0013	3.69E-05				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Weighted Median	0.0052	0.0013	4.51E-05				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Egger Slope	0.0064	0.0043	0.137				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Egger Intercept	-0.0001	0.0021	0.962				
Directional MR Steiger filtering + LD SNP removed														
201529	381833[c]	SBP, Corrected	Albuminuria	46	NA	rs3735533	Two-Stage Least-Squares	0.0045	0.0007	6.26E-11				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	IVW Random Effects	0.0048	0.0014	4.82E-04	135	7E-11	141	< 1E-5
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Simple Median	0.0051	0.0013	5.48E-05				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Weighted Median	0.0051	0.0013	5.99E-05				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Egger Slope	0.0023	0.0049	0.629				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Egger Intercept	0.0013	0.0024	0.598				
Diastolic Blood Pressure														
Directional MR Steiger filtering														
201529	381833[c]	DBP, Corrected	Albuminuria	52	NA	NA	Two-Stage Least-Squares	0.0070	0.0012	1.83E-09				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	IVW Random Effects	0.0071	0.0025	3.81E-03	192	4E-18	199	< 1E-5
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Simple Median	0.0053	0.0021	0.011				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Weighted Median	0.0075	0.0021	2.90E-04				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Egger Slope	0.0067	0.0090	0.457				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Egger Intercept	0.0001	0.0027	0.958				
Directional MR Steiger filtering + Outlier removed														
201529	381833[c]	DBP, Corrected	Albuminuria	51	0.37	NA	Two-Stage Least-Squares	0.0085	0.0012	6.66E-13				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	IVW Random Effects	0.0086	0.0022	8.46E-05	145	4E-11	150	< 1E-5
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Simple Median	0.0054	0.0021	0.011				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Weighted Median	0.0086	0.0021	3.38E-05				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Egger Slope	0.0106	0.0079	0.181				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Egger Intercept	-0.0006	0.0024	0.794				
Directional MR Steiger filtering + LD SNP removed														
201529	381833[c]	DBP, Corrected	Albuminuria	51	NA	rs3735533	Two-Stage Least-Squares	0.0062	0.0012	1.17E-07				
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	IVW Random Effects	0.0063	0.0023	0.007	167	2E-14	174	< 1E-5
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Simple Median	0.0051	0.0021	0.015				
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Weighted Median	0.0068	0.0021	9.76E-04				

201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Egger Slope	0.0030	0.0085	0.723
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Egger Intercept	0.0010	0.0026	0.687

SBP, systolic blood pressure; DBP, diastolic blood pressure. Corrected, corrected for hypertensive medication use.

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

[a] Effects on blood pressure were calculated in up to 201529 individuals in the International Consortium for Blood Pressure Cardio-MetaboChip study (Ehret *et al* 2016. Nature Genetics. PMID 27618452)

[b] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank (not applicable for two-stage least-squares regression)

[c] 381833 individuals in UK Biobank had both albuminuria and blood pressure measurements required for two-stage least-squares regression

Table S10. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score in UK Biobank with blood pressure in ICBP 1000G.

Sample Size, Exposure[a]	Sample Size, Outcome[b]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure													
Directional MR Steiger filtering													
382500	150134	Albuminuria	SBP, Corrected	37	NA	IVW Fixed Effects	2.689	0.768	4.64E-04				
382500	150134	Albuminuria	SBP, Corrected	37	NA	IVW Random Effects	2.689	1.162	0.021	82	2E-05	110	< 1E-05
382500	150134	Albuminuria	SBP, Corrected	37	NA	Simple Median	2.792	1.260	0.027				
382500	150134	Albuminuria	SBP, Corrected	37	NA	Weighted Median	2.639	1.325	0.046				
382500	150134	Albuminuria	SBP, Corrected	37	NA	Egger Slope	0.045	2.588	0.986				
382500	150134	Albuminuria	SBP, Corrected	37	NA	Egger Intercept	0.055	0.048	0.253				
Directional MR Steiger filtering + Outlier removed													
382500	150134	Albuminuria	SBP, Corrected	36	0.44	IVW Fixed Effects	3.457	0.784	1.05E-05				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	IVW Random Effects	3.457	1.019	6.92E-04	59	0.007	78	0.0003
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Simple Median	3.708	1.241	0.003				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Weighted Median	2.657	1.316	0.044				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Egger Slope	1.218	2.246	0.588				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Egger Intercept	0.046	0.041	0.264				
Diastolic Blood Pressure													
Directional MR Steiger filtering													
382500	150134	Albuminuria	DBP, Corrected	35	NA	IVW Fixed Effects	1.033	0.477	0.030				
382500	150134	Albuminuria	DBP, Corrected	35	NA	IVW Random Effects	1.033	0.775	0.183	90	6E-07	118	< 1E-05
382500	150134	Albuminuria	DBP, Corrected	35	NA	Simple Median	3.093	0.798	1.06E-04				
382500	150134	Albuminuria	DBP, Corrected	35	NA	Weighted Median	0.854	0.805	0.289				
382500	150134	Albuminuria	DBP, Corrected	35	NA	Egger Slope	-0.442	1.732	0.799				
382500	150134	Albuminuria	DBP, Corrected	35	NA	Egger Intercept	0.031	0.033	0.341				
Directional MR Steiger filtering + Outlier removed													
382500	150134	Albuminuria	DBP, Corrected	34	0.45	IVW Fixed Effects	1.552	0.487	0.001				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	IVW Random Effects	1.552	0.677	0.022	64	0.001	83	2E-05
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Simple Median	3.127	0.786	6.94E-05				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Weighted Median	0.897	0.789	0.255				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Egger Slope	0.316	1.494	0.833				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Egger Intercept	0.026	0.028	0.353				

SBP, systolic blood pressure; DBP, diastolic blood pressure. Corrected, corrected for hypertensive medication use.

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

[a] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank

[b] Effects of SNPs on blood pressure were calculated in up to 150534 individuals in the International Consortium for Blood Pressure 1000G imputation (Wain *et al* 2017. Hypertension. PMID 28739976)

Table S11. Genome-wide association study of albuminuria in 302687 individuals in UK Biobank without hypertensive medication use

Lead variant	Nearest Gene(s)	Description	Chr	Position (hg19)	Effect Allele	Noneffect Allale	EAF	Beta (log(mg/g))	SE (log(mg/g))	P value
rs10157710	*FOXD2-TRABD2B*	Intergenic	1	47961691	T	C	0.802	0.01599	0.00219	3.02E-13
rs4665972	*SNX17*	Intronic, noncoding RNA variant	2	27598097	T	C	0.392	0.01104	0.00180	8.28E-10
rs6712846	*CPO-KLF7*	Intergenic	2	207889080	A	G	0.525	0.00954	0.00175	4.88E-08
rs1047891	*CPS1*	Missense	2	211540507	C	A	0.683	0.01031	0.00188	3.98E-08
rs183131780	*NYAP2-LOC646736*	Intergenic	2	226684886	T	C	0.002	0.13566	0.02080	6.99E-11
rs35483183	*COL4A4*	Intronic	2	227876687	A	G	0.123	0.01502	0.00268	1.98E-08
rs35924503	*SPHKAP-PID1*	Intergenic	2	229131286	C	T	0.001	0.17391	0.02693	1.06E-10
rs7670121	*NR3C2*	Intronic, noncoding RNA variant	4	149128595	G	A	0.240	0.01161	0.00205	1.36E-08
rs189107782	*LINC01262-FRG1*	Intergenic	4	190729009	T	C	0.002	0.20163	0.02131	3.11E-21
rs7731168	*CWC27*	Intronic	5	64296471	C	G	0.233	0.01183	0.00207	1.09E-08
rs4410790	*AGR3-AHR*	Intergenic	7	17284577	C	T	0.633	0.01595	0.00181	1.35E-18
rs4738817	*CHD7*	Intronic	8	61620613	G	A	0.549	0.00976	0.00176	2.73E-08
rs28601761	*TRIB1-LINC00861*	Intergenic	8	126500031	C	G	0.579	0.01059	0.00179	3.26E-09
rs45551835	*CUBN*	Missense	10	16932384	A	G	0.014	0.11178	0.00739	1.15E-51
rs144360241	*CUBN*	Missense	10	16967417	C	T	0.005	0.07690	0.01303	3.60E-09
rs141640975	*CUBN*	Missense	10	16992011	A	G	0.003	0.33405	0.01718	3.35E-84
rs2236295	*ADO*	Missense, TFBS variant, Regulatory region variant	10	64564892	G	T	0.593	0.01020	0.00178	1.10E-08
rs67339103	*C10orf11*	Intronic, noncoding RNA variant	10	77893686	A	G	0.213	0.01328	0.00215	6.02E-10
rs2601006	*CCT2*	5' UTR variant, Intronic	12	69979517	C	T	0.657	0.01086	0.00184	3.55E-09
rs3759794	*LTK*	Upstream variant, Regulatory region variant	15	41806658	G	A	0.883	0.01553	0.00272	1.17E-08
rs16943246	*C15orf48*	Upstream variant	15	45720597	G	A	0.753	0.01155	0.00203	1.30E-08
rs2470893	*CYP1A1*	Upstream variant	15	75019449	T	C	0.335	0.01495	0.00185	5.87E-16
rs838142	*FUT1*	3' UTR Variant	19	49252151	A	G	0.723	0.01189	0.00196	1.21E-09

Chr, chromosome; EAF, effect allele frequency. For intergenic loci, nearest upstream and downstream RefSeq genes are indicated. Nearest gene should not be taken as evidence of causal gene. Description indicates VEP most severe consequences of nearest gene and any regulatory annotations associated with lead variant

Table S12. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score with blood pressure in UK Biobank participants not on anti-hypertensive medications.

Sample Size[a]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure												
Directional MR Steiger filtering												
302687	Albuminuria	Systolic BP	22	NA	Two-Stage Least-Squares	1.455	0.472	0.002				
302687	Albuminuria	Systolic BP	22, unweighted allele score	NA	Two-Stage Least-Squares	2.904	0.665	1.27E-05				
302687	Albuminuria	Systolic BP	22	NA	IVW Random Effects	1.455	0.873	0.096	71	2E-07	80	< 1E-05
302687	Albuminuria	Systolic BP	22	NA	Simple Median	2.443	0.862	0.005				
302687	Albuminuria	Systolic BP	22	NA	Weighted Median	0.415	0.779	0.594				
302687	Albuminuria	Systolic BP	22	NA	Egger Slope	0.004	1.179	0.997				
302687	Albuminuria	Systolic BP	22	NA	Egger Intercept	0.054	0.031	0.082				
Directional MR Steiger filtering + Outlier removed												
302687	Albuminuria	Systolic BP	21	0.78	Two-Stage Least-Squares	2.224	0.550	5.21E-05				
302687	Albuminuria	Systolic BP	21	0.78	IVW Random Effects	2.224	0.985	0.024	64	2E-06	69	< 1E-05
302687	Albuminuria	Systolic BP	21	0.78	Simple Median	2.453	0.910	0.007				
302687	Albuminuria	Systolic BP	21	0.78	Weighted Median	2.433	0.877	0.006				
302687	Albuminuria	Systolic BP	21	0.78	Egger Slope	0.817	1.661	0.623				
302687	Albuminuria	Systolic BP	21	0.78	Egger Intercept	0.039	0.037	0.293				
Diastolic Blood Pressure												
Directional MR Steiger filtering												
302687	Albuminuria	Diastolic BP	22	NA	Two-Stage Least-Squares	0.672	0.272	0.014				
302687	Albuminuria	Diastolic BP	22, unweighted allele score	NA	Two-Stage Least-Squares	1.015	0.384	0.008				
302687	Albuminuria	Diastolic BP	22	NA	IVW Random Effects	0.672	0.494	0.174	69	5E-07	76	< 1E-05
302687	Albuminuria	Diastolic BP	22	NA	Simple Median	0.898	0.483	0.063				
302687	Albuminuria	Diastolic BP	22	NA	Weighted Median	0.465	0.430	0.280				
302687	Albuminuria	Diastolic BP	22	NA	Egger Slope	0.329	0.708	0.643				
302687	Albuminuria	Diastolic BP	22	NA	Egger Intercept	0.013	0.019	0.493				
Directional MR Steiger filtering + Outlier removed												
302687	Albuminuria	Diastolic BP	21	0.47	Two-Stage Least-Squares	1.010	0.317	0.001				
302687	Albuminuria	Diastolic BP	21	0.47	IVW Random Effects	1.010	0.570	0.077	65	1E-06	70	< 1E-05
302687	Albuminuria	Diastolic BP	21	0.47	Simple Median	1.088	0.513	0.034				
302687	Albuminuria	Diastolic BP	21	0.47	Weighted Median	1.191	0.498	0.017				
302687	Albuminuria	Diastolic BP	21	0.47	Egger Slope	0.950	0.989	0.337				
302687	Albuminuria	Diastolic BP	21	0.47	Egger Intercept	0.002	0.022	0.940				

BP, blood pressure

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

[a] Effects of SNPs on both albuminuria and blood pressure were measured in 302687 individuals in UK Biobank who had both albuminuria and blood pressure measurements and were not taking blood pressure medications

Table S13. Power to Detect Significant Associations between Albuminuria Risk Score and Cardiometabolic Disease

Disease	Cases, UK Biobank	Controls, UK Biobank	Causal Effect (Odds Ratio)	R^2 variance explained by Albuminuria Risk Score in UK Biobank	Power to Detect
All-Cause Mortality	11087	371413	1.1	0.007	**0.12**
			1.2	0.007	**0.35**
Coronary Artery Disease	32623	349877	1.1	0.007	**0.28**
			1.15	0.007	**0.52**
			1.2	0.007	**0.75**
Stroke	8818	373682	1.1	0.007	**0.11**
			1.15	0.007	**0.19**
			1.2	0.007	**0.29**
Peripheral Vascular Disease	4543	377957	1.2	0.007	**0.17**
			1.3	0.007	**0.31**
Heart Failure	5737	376503	1.1	0.007	**0.08**
			1.2	0.007	**0.21**
			1.3	0.007	**0.38**
			1.4	0.007	**0.56**
Type 2 Diabetes	17619	364881	1.2	0.007	**0.51**
Chronic Kidney Disease	4885	377615	1.1	0.007	**0.08**
			1.2	0.007	**0.18**
			1.3	0.007	**0.33**
			1.4	0.007	**0.5**
			1.5	0.007	**0.65**
Hypertension	124345	258155	1.1	0.007	**0.64**
			1.2	0.007	**0.99**

Causal effect values based on the range of observational or Mendelian randomization associations